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PATENT SPECIFICATION

NO DRAWINGS

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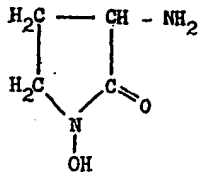
COMPLETE SPECIFICATION

Pyrrolidone Derivatives and Pharmaceutical preparations containing them

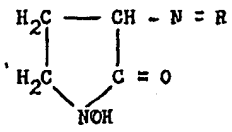
We, ORGANON LABORATORIES LIMITED, a British Company, of Crown House, London Road, Morden, Surrey, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pyrrolidone derivatives and pharmaceutical preparations containing them.

In Collection Czechoslov. Chem. Commun. *24*, 1672—1676 (1959) there is described the preparation of a pyrrolidone derivative having the formula —



It has now been found unexpectedly that this pyrrolidone derivative, together with other similar compounds which have not previously been prepared and which are described below, has valuable pharmaceutical properties in that it has a depressant action on the central nervous system while being of low toxicity. Accordingly, the present invention is directed to pharmaceutical preparations having a depressant action on the central nervous system which comprise a mixture of a pharmaceutically-acceptable carrier medium and a compound of the general formula—



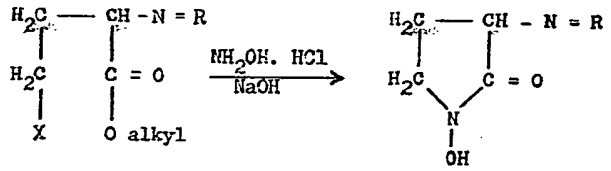
in which —N=R represents an amino, dialkylamino, acylamino or morpholino group, the preparation being in the form of ampoules or solid dosage units (such as tablets, pills and suppositories) each containing 5—500 mg. of the said compound.

Tests made with compounds of the formula given above have shown that, in mice, the active and the lethal dose are in the ratio of 1:30. The action of the compounds on the central nervous system is selective so that on administration there occur no undesired side effects on the respiratory and circulation functions. The compounds are very active, both on oral and on parenteral administration. Owing to their favourable properties they are especially useful in the treatment of various kinds of

epilepsy and Parkinson's disease. The compound 1-hydroxy-3-amino-pyrrolidone-2 in particular possesses a very strong anti-tremor activity.

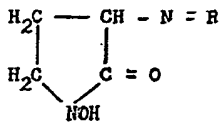
As stated above, the present preparations are prepared in solid dosage unit forms or in the form of ampoules each containing 5—500 mg. of the active compound. A very suitable dosage unit contains 40—400 mg. of the active substance. The pharmaceutically-acceptable carrier medium or vehicle used in the preparations can be lactose, starch, sugar or dextrin, together with other conventional excipients, such as stearic acid, magnesium stearate and gelatin. Solid dosage unit forms may be administered rectally, using in this case auxiliarics suitable for this form of administration.

The active compounds of the present invention can be prepared according to the following reaction—



in which X represents a chlorine, iodine or bromine atom, and —N=R has the meaning previously given. The hydroxamic acid which is formed as an intermediate product is not shown in the equation.

As indicated already, some of these compounds have not previously been prepared. The invention accordingly extends to new compounds of the general formula—



in which —N=R represents a dialkylamino, acylamino or morpholino group.

Clinical investigations with solid dosage units containing 1-hydroxy-3-amino-pyrrolidone-2 yielded the following favourable results. To 18 patients all showing a distinct tremor, solid dosage units giving 3 x 100 mg of the said compound were orally administered daily for two weeks. Thirteen cases of extra pyramidal tremor reacted most favourably to this treatment, for there occurred a strong reduction of the tremor and no undesirable side-effects were observed.

After treatment of 4 patients suffering from Parkinson's disease with solid dosage units giving 2 to 3 x 100 mg of the said compound daily, a distinct reduction of the tremor with no undesirable side-effects was noticed after 14 days.

The manufacture of pharmaceutical preparations in accordance with the invention is further illustrated in the following Examples I to V.

EXAMPLE I.

75 g. of lactose are mixed with a solution of 0.75 g. of gelatin in 7.5 ml. of water. The mixture is processed to a dry granulate. To this granulate 25 g. of 1-hydroxy-3-amino-pyrrolidone-2, 1.5 g. of stearic acid, 20 g. of potato starch and 27.75 g. of talc are added. After mixing the mass obtained is tableted into 500-mg. tablets each containing about 80 mg. of the active compound.

EXAMPLE II.

Mix 81.5 g. of lactose and 25 g. potato starch with a solution of 1.0 g. of gelatin in 10 ml. of water. The mixture is processed into a dry granulate, which is mixed with 100 g. of 1-hydroxy-3-dimethylaminopyrrolidine-2, 25 g. of potato starch, 25 g. of stearic acid and 12.5 g. of talc. The resulting mixture is tableted into 250-mg. tablets each containing 100 mg. of the active compound.

EXAMPLE III.

Tablets are made as indicated in example I, but this time the mass is tableted into 100-mg. tablets each containing about 16 mg. of the active compound.

EXAMPLE IV.

Tablets are made in accordance with example I, but in these tables 1-hydroxy-3-morpholino-pyrrolidone-2 is used as the active substance.

EXAMPLE V.

A solution is prepared of 25 g. of 1-hydroxy-3-aminopyrrolidone-2 in 1 l. of

distilled pyrogen-free water. To the resulting solution sodium chloride is added till the solution is isotonic. The liquid is filled into 2-ml. ampoules, after which these ampoules are sterilised. Each ampoule contains 50 mg of the active compound.

In three of these Examples, namely Examples I, III and V, the active substance in the preparations is 1-hydroxy-3-amino-pyrrolidone-2. This can be prepared in the following manner:

At a temperature of $-5°C$, 5.6 g. of the hydrochloride of methyl α-amino-γ-chloro-butyrate [prepared according to Frankel and Knobber, J.Am.Soc. *80*, 3147 (1958)] are added to a mixture of 5.2 g. of sodium hydroxide, 3.1 g. of hydroxylamine hydrochloride and 11.3 ml. of distilled water. The reaction mixture is stirred for 3 hours at 0°C and after that for 1 hour at 30°C. After cooling to $-10°C$ the pH is adjusted to a value of 5.6 with hydrochloric acid, whereupon 6.3 g. of di-ethylamine are added.

For removal of inorganic salts the reaction mixture is next poured into 150 ml. of absolute alcohol at 60°C and kept at this temperature for 15 minutes. After cooling to 0°C the mixture is filtered, after which the filtrate is adjusted to pH 6 with glacial acetic acid. The resulting precipitate is filtered off, washed with alcohol and ether and dried in vacuo over P_2O_5. After recrystallising a few times from ethanol the melting point of the resulting 1-hydroxy-3-amino-pyrrolidone-2 is 184°C (decomposition).

The manufacture of other active substances for use in preparations in accordance with the invention is illustrated by the following Examples VI to X.

EXAMPLE VI.

1-hydroxy-3-benzoylamino-pyrrolidone-2.

In the same manner as described above in connection with 1-hydroxy-3-amino-pyrrolidone-2, the substance 1-hydroxy-3-benzoylamino-pyrrolidone-2 is prepared starting from methyl α-benzoylamino-γ-bromo-butyrate.

EXAMPLE VII.

1-hydroxy-3-acetylamino-pyrrolidone-2.

In the same manner as described above in connection with 1-hydroxy-3-amino-pyrrolidone-2, the substance 1-hydroxy-3-acetylamino-pyrrolidone-2 with melting point 148.5°—150.5°C is prepared starting from methyl α-acetylamino-γ-chloro-butyrate.

EXAMPLE VIII.

In the same manner as described above in connection with 1-hydroxy-3-amino-pyrrolidone-2, the substance 1-hydroxy-3-morpholino-pyrrolidone-2 is prepared starting from methyl α-morpholino-γ-chloro-butyrate.

EXAMPLE IX.

In the manner as described above in connection with 1-hydroxy-3-amino-pyrrollidone-2, the substance 1-hydroxy-3-dimethylamino-pyrrolidone-2 with melting point 124.0°—126.5°C is prepared starting from methyl α-dimethylamino-γ-chloro-butyrate.

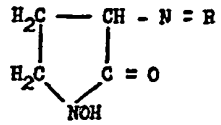
EXAMPLE X.

1-hydroxy-3-glycylamino-pyrrolidone-2.

Benzyloxycarbonylglycine (4.8 gm.) was dissolved in 25 ml. of tetrahydrofuran. After cooling down to a temperature of $-40°C$ 2.74 ml. of N-ethylpiperidine were added while stirring and next 1.91 ml. of ethyl chloroformate. After that the temperature was raised to $-10°C$ which temperature was maintained for 15 minutes. Next the mixture was cooled down to $-40°C$ and the precipitate formed, consisting of N-ethylpiperidine HCl, filtered off. At $-20°C$ a pre-cooled solution of 2.78 gm. of 1-hydroxy-3-amino-pyrrolidone-2 and 3.28 ml. of N-ethylpiperidine dissolved in 20 ml. of water was added to the filtrate. Next the temperature of the reaction mixture was raised to room temperature, which temperature was maintained for 2 hours. Next the solvent was entirely evaporated. The residue was taken up in 100 ml. of water and purified over an acid ion exchanger. Finally the 1-hydroxy-3-(benzyloxycarbonyl-glycyl) amino-pyrrolidone-2 was obtained from the eluate in 1.62 gm. yield by lyophilisation. By means of palladium and hydrogen the benzyloxycarbonyl group was split off to obtain 0.90 gm. of the final product. After recrystallisation from absolute alcohol the compound showed an R_f of 0.13 in a mixture of butanol-acetic acid-water (4:1:5).

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation having a depressant action on the central nervous system which comprises a mixture of a pharmaceutically-acceptaable carrier medium and a compound of the general formula

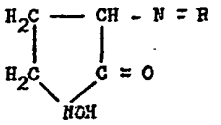


in which —N=R represents an amino, dialkylamino, acylamino or morpholino group, the preparation being in the form of ampoules or solid dosage units (such as tablets, pills and suppositories) each containing 5—500 mg of the said compound.

2. A pharmaceutical preparation according to claim 1, in which each solid dosage unit or ampoule contains 1-hydroxy-3-amino-pyrrolidone-2.

3. A pharmaceutical preparation according to claim 1 or claim 2, in which each solid dosage unit or ampoule contains 40—400 mg. of 1-hydroxy-3-amino-pyrrolidone-2.

4. A compound of the general formula—



in which —N=R represents a dialkylamino, acylamino or morpholino group.

5. 1-hydroxy-3-benzoylamino-pyrrolidone-2.

6. 1-hydroxy-3-glycylamino-pyrrolidone-2.

7. 1-hydroxy-3-dimethylamino-pyrrolidone-2.

8. A pharmaceutical preparation according to claim 1, substantially as herein described with reference to any one of the foregoing Examples I to V.

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